Understanding the cause of type 2 diabetes

Roy Taylor

Type 2 diabetes has long been thought to have heterogenous causes, even though epidemiological studies uniformly show a tight relationship with overnutrition. The twin cycle hypothesis postulated that interaction of self-reinforcing cycles of fat accumulation inside the liver and pancreas, driven by modest but chronic positive calorie balance, could explain the development of type 2 diabetes. This hypothesis predicted that substantial weight loss would bring about a return to the non-diabetic state, permitting observation of the pathophysiology determining the transition. These changes were postulated to reflect the basic mechanisms of causation in reverse. A series of studies over the past 15 years has elucidated these underlying mechanisms. Together with other research, the interaction of environmental and genetic factors has been clarified. This knowledge has led to successful implementation of a national programme for remission of type 2 diabetes. This Review discusses the paucity of evidence for heterogeneity in causes of type 2 diabetes and summarises the in vivo pathophysiological changes, which cause this disease of overnutrition. Type 2 diabetes has a homogenous cause expressed in genetically heterogenous individuals.

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Introduction

Type 2 diabetes affects 4·4 million adults in the UK and 508 million people worldwide, with major medical, social, and economic implications.[1,2] Defining the cause of this modern epidemic is important both for prevention and management of the condition. Type 2 diabetes is widely considered to have heterogenous causes,[3–5] despite no clear evidence and epidemiological studies showing an absolute relationship with food availability. Although the basic physiology underpinning most bodily systems is well established, a wider understanding of glucose metabolism requires in vivo magnetic resonance techniques for the study of intraorgan substrates. Application of these techniques during transition between the diabetic and non-diabetic states in humans has now revealed the underlying mechanisms causing type 2 diabetes. This Review aims to set in context this new knowledge.

Consideration of heterogeneity

The range of putative causes of type 2 diabetes is summarised in the table. The overall impression of complexity tends to conceal the small or inapparent effect size of some factors. The hypothesis that bacteria in the large intestine could affect metabolic function and contribute to heterogeneity of type 2 diabetes has attracted much attention. Epidemiological studies show associations between the microbiome and type 2 diabetes but much evidence suggests no causal relationship.[20–25] Obesity is frequently assumed to be a cause of type 2 diabetes, with the wide range of bodyweights at diagnosis being regarded an indicator of heterogeneity. It has become accepted that people with type 2 diabetes who do not have obesity have less insulin resistance but a greater β-cell defect than those with overweight or obesity.[6–9,69] However, insulin resistance rises in step with adiposity itself and the important comparison is with BMI-matched normoglycaemic controls. Such studies have shown that the degree of insulin resistance in groups with and without obesity and type 2 diabetes is similarly raised compared with BMI-matched control groups.[14] Crucially, in type 2 diabetes, test meals elicit similar increases over basal of plasma C-peptide in people with obesity (1·8-fold) and without obesity (2·5-fold).[16] The first-phase insulin response is minimal or absent in type 2 diabetes across the BMI range.[16]

Six distinct subgroups of diabetes have been suggested by clustering of phenotypic characteristics.[67] These analyses group together all with a diagnosis of diabetes including type 1 diabetes. However, almost a quarter of individuals change their classification over 5 years, a regrouping not related to cause at presentation.[68] Monogenic diabetes, causally distinct from type 2 diabetes, is not identified by the clustering technique.[67] Such large studies will not exclude people who have non-type 2 diabetes causes for their diabetes and these are likely to be over-represented in distinguished clusters. If complications are included in phenotypic characteristics, more genetic clusters are identified.[70] Specific genes linked with underlying conditions such as body fat distribution or BMI have already been identified.[71,72] In common diseases, genes most often confer polygenic susceptibility rather than direct causation. It is useful to consider that phenotypic expression of disease can vary widely in conditions of a known single cause. Individuals respond differently to identical challenges because of differing genotype. For instance, the specific virus-causing influenza might bring about a range of syndromes from mild coryza to fatal pneumonitis, but study of groups presenting with specific clinical patterns of influenza would not contribute to understanding its cause. Hence, genetic study of clustering of characteristics can provide useful insight into degrees of likelihood of expressing various clinical phenotypes, but not necessarily into causes.

Changes in prevalence in populations

The link between type 2 diabetes and nutrition is illustrated by the sharp decrease in type 2 diabetes incidence during food shortage brought about by war or economic collapse.[73,74] Joslin[75] and Hrdlička[76] observed the absence of diabetes in Pima Indians when living as subsistence farmers, yet subsequent overnutrition

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	Supporting evidence	Negating evidence
Obesity	Increased prevalence of BMI of 30 kg/m². Relationship with insulin resistance and secretion.[6-9]	Type 2 diabetes occurs in populations without obesity.[10-12] Most people with obesity do not have type 2 diabetes.[13] No difference in relative insulin resistance and secretion when compared with BMI-matched normoglycaemic controls.[14,15] First-phase insulin secretion is severely impaired across the BMI range.[16] Weight loss causes remission irrespective of BMI.[17-19]
Microbiome	Epidemiological associations.[20-25]	No consistent relationship between specific taxa and disease.[21] Different taxa are associated in different geographical locations.[22] No direct links with metabolic factors in humans when compared with rodents.[23] No metabolic effect of prebiotics or probiotics in humans.[20,24]
Incretin deficiency	GLP-1 spike after bariatric surgery associated with decreased plasma glucose.[26]	Decrease in plasma glucose after food restriction mimicking post bariatric surgery produces the same or better plasma glucose improvement. Insulin secretion is not enhanced by the incretin spike post bariatric surgery.[27,28]
Inflammation	Increased plasma TNFα and IL-6 are thought to impair insulin sensitivity and β-cell function.[29] Neutralisation of plasma TNF in rodents is reported to decrease glucose.[30] Inflammation is shown in subcutaneous adipose tissue.[31] Plasma IL-1 receptor agonists are increased before diagnosis of type 2 diabetes[32]	Increase in plasma markers is minimal in people with type 2 diabetes compared with the concentration required to cause insulin resistance.[19,33] No increase in total inflammatory cells in human islets.[34] Complete removal of TNF in people with type 2 diabetes causes no change in plasma glucose.[35] No abnormality in high-sensitivity C-reactive protein concentrations during transition from type 2 diabetes to a non-diabetic state in the absence of obesity.[19] Plasma IL-1 receptor agonists reflect obesity-related inflammation in adipose tissue rather than a specific type 2 diabetes marker.[36]
Adiponectin	Association with future risk of type 2 diabetes.[37] Possible component of appetite drive to positive energy balance.	Strong marker for insulin sensitivity itself and affected by BMI.[37] Difference between women and men in association with future risk.[37]
Amyloid	More frequently found in human type 2 diabetes islets, suggesting impairment of β-cell function.[38]	Found in other causal types of diabetes.[39] Rapid recovery of acute insulin response with weight loss.[40]
Apoptosis and low β-cell mass	Low β-cell number on immunohistology at diagnosis.[7,41]	Full recovery of functional β-cell capacity during long-term remission despite minimal regenerative capacity in adults.[42] No excess lipofuscin bodies at post-mortem.[43]
Hyperfunction and exhaustion	Increased basal insulin secretion during prediabetes and early type 2 diabetes that leads to β-cell failure.[44]	Weight loss induces recovery in prediabetes[45] and type 2 diabetes.[42]
Mitochondrial defect	Smaller mitochondria in skeletal muscle.[46,47] Decreased ATP turnover in skeletal muscle is said to contribute to insulin resistance.[48-50]	Less glycogen synthesis in insulin-resistant muscle requires less ATP.[51] Defect is secondary to hyperglycaemia as it is not present when glucose is <8 mmol/L.[52]
Molecular defects of insulin signalling	In vitro studies and rare syndromes cause impairment of transmission of the insulin signal and thus insulin resistance.[53]	Genome-wide studies find no consistent links with known defects.[54,55] Nine of ten people return to the non-diabetic state after 15 kg weight loss.[56]
Plasma fatty acid oversupply	Infusion causes insulin resistance in muscle and decreased acute insulin response.[57-59] Saturated long-chain fatty acids have potent effects both in vitro and in vivo.[60,61] Molecular mechanism of the effect on β cells is established.[62,63]	Plasma fatty acid concentrations are only slightly raised in early type 2 diabetes.[61,64] The major source for tissues is VLDL triglyceride, rather than plasma fatty acids.[65]
Oxidative stress	In vitro observations suggest damage to β cells.[66]	Can be induced by fatty acid oversupply.[62]
Factors underlying clustering of phenotypic characteristics	Analysis of phenotypic characteristics shows clustering of people with type 2 diabetes.[67]	25% of individuals change groupings over time.[68] No pathophysiological basis identified for existence of causal subtypes of type 2 diabetes.

Table: **Summary of postulated causes of type 2 diabetes**

revealed susceptibility to type 2 diabetes in 40% of this population.[77] In 2006, genetically similar Pima Indians who migrated to Mexico and were exposed to less abundant food had a prevalence of 7% compared with 38% of those living in the USA.[78] Although there must be an underlying genetic basis for the high susceptibility to type 2 diabetes in this population, these data show that expression of disease is conditional upon lifestyle. This fact is well established for prediabetes, the earliest stage in developing type 2 diabetes, a condition that can be reversed by weight loss however achieved.[45]

A major factor preventing the application of these epidemiological observations to understanding type 2 diabetes has been the incomplete knowledge of the physiology of food handling in the body, which has had to await the development of magnetic resonance imaging techniques that permit real-time measurement of substrate handling inside the major organs.

The pathophysiological basis

The earliest indicator of increased risk of type 2 diabetes is insulin resistance in muscle, a familial characteristic.[50,79,80] The everyday practical effect of muscle insulin resistance is the minimal storage of meal-derived carbohydrate as muscle glycogen.[81] In people with muscle insulin resistance, less than 10% of meal carbohydrate is stored in skeletal muscle within 5 h of eating compared with over 30% in people with higher muscle insulin sensitivity.[82,83] Muscle glycogen concentrations peak around 5 h after a meal[82] and, during a typical day of eating, rise sequentially after each meal.[83,84] Overnight, concentrations decrease back to the fasting baseline, most likely by exporting lactate to the liver to supply gluconeogenesis.[85] Hence, skeletal muscle acts as a dynamic buffer contributing to the maintenance of plasma glucose within narrow limits. The postprandial storage of glycogen in the liver is determined by the rate

of glucose delivery and is similar in people with or without type 2 diabetes and non-diabetic controls.[84]

The glucose not stored in muscle has to be diverted into the alternative pathway of glucose conversion to fat via de novo lipogenesis.[50,86] De novo lipogenesis produces palmitic acid only, a saturated fatty acid, which is the most potent fatty acid in decreasing β-cell function.[87,88] The insulin resistance in muscle is present from early life and is mediated by impaired glucose transport. In contrast, glucose in hepatocytes fluxes freely across the cell membrane and liver insulin resistance is determined by liver fat content.[89,90] Plasma glucose control is maintained in the face of insulin resistance in both organs provided that the pancreas remains able to compensate by increasing insulin secretion rates.

Estimated β-cell function has decreased to around 50% of typical rates by the time of diagnosis of type 2 diabetes and continues to decline linearly irrespective of conventional pharmacological treatments.[91,92] The table lists postulated underlying causes; however, little attention has been paid to the observations of McGarry[93] who first highlighted the potential for excess fatty acid supply as a cause of β-cell dysfunction. This observation was confirmed in a rodent model by Unger and colleagues[94] who showed that islets isolated from young rats genetically prone to overfeeding-induced diabetes displayed a typical acute response to sudden increase in glucose concentration. However, if exposed to a low concentration (ie, 0·2 mmol/L) of palmitic acid during a 7-day preincubation, the acute response to elevated glucose was abolished. In contrast, islets taken from littermates, not genetically susceptible to overfeeding-induced diabetes (Zucker rats heterozygous for the fa gene), were completely unaffected by such fatty acid exposure.

These seminal studies show that β-cell function in vivo can be suppressed by prolonged exposure to excess fatty

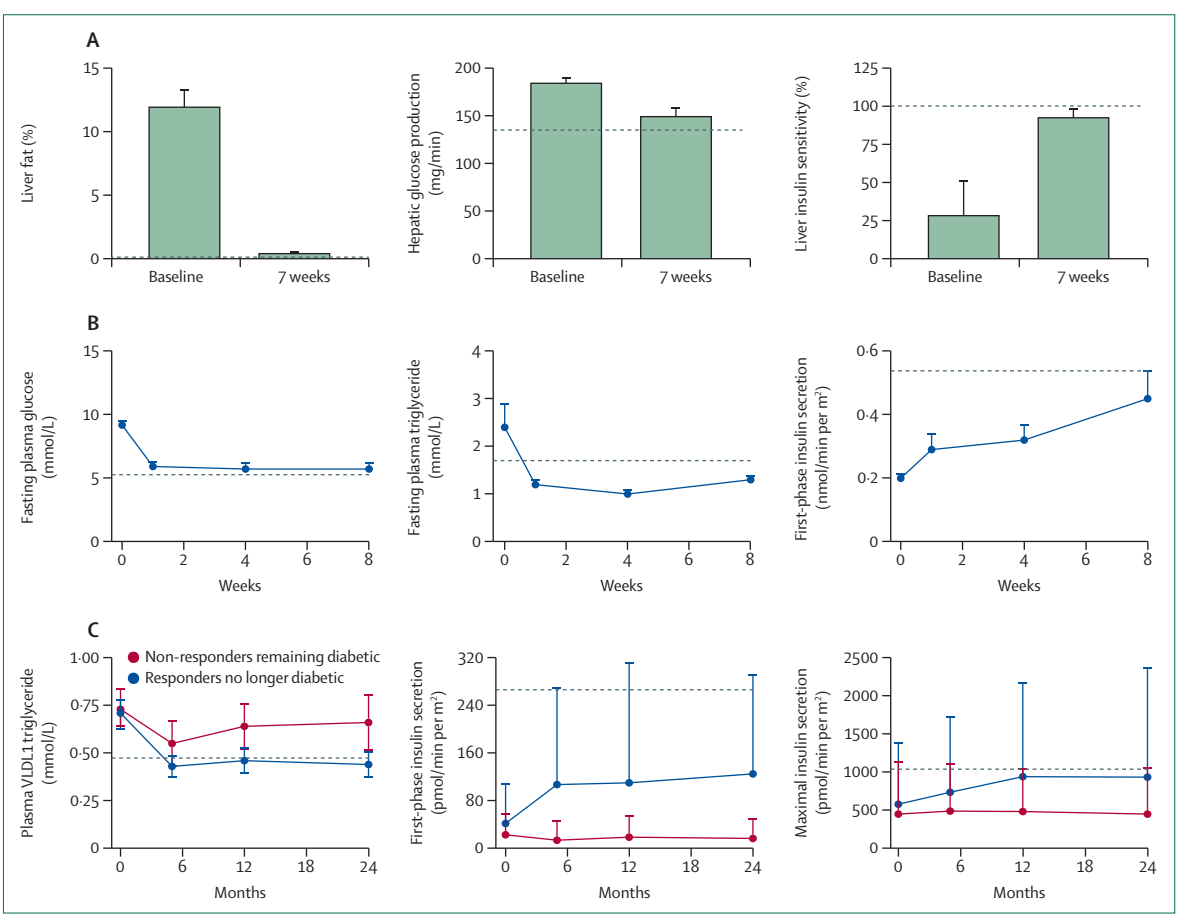

Figure 1: **Key pathophysiological data from studies of weight loss in people with type 2 diabetes**
(A) Weight loss averaging 8 kg in type 2 diabetes brought about a dramatic normalisation of liver fat content, return to non-diabetic fasting hepatic glucose production, and complete correction of the previously severe hepatic insulin resistance. Reproduced from Peterson et al,[89] by permission of the authors. (B) Weight loss averaging 15 kg in type 2 diabetes normalised fasting plasma glucose and triglyceride within 7 days by the same mechanisms shown above, and over 8 weeks gradually increased first-phase β-cell insulin response towards rates in the non-diabetic control group.[40] (C) A 2-year study showed the sustained return to non-diabetic fasting plasma triglyceride (dashed line) in those who reached remission (closed circles), improvement in first-phase insulin response, and gradual return to non-diabetic rates over 12 months in maximal insulin response reflecting functional β-cell mass.[61] Dashed lines show mean level in matched groups with normal glucose tolerance.

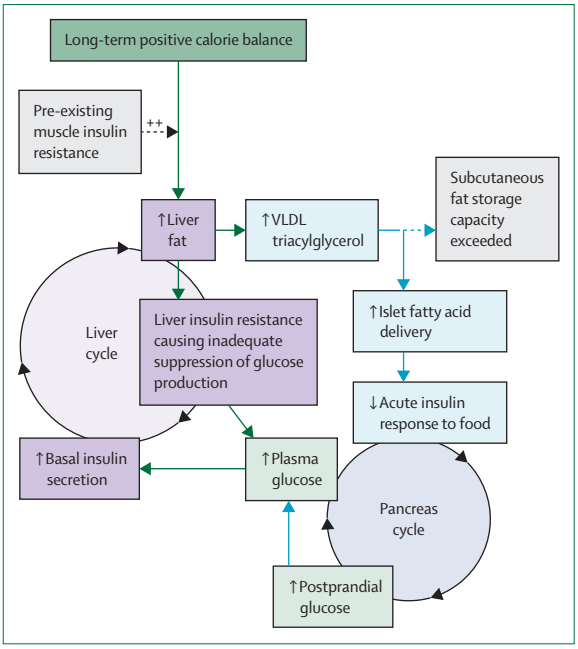

Figure 2: **The twin cycle hypothesis**
This hypothesis postulated that intake of more food energy than required over a long period of time would lead to increased liver fat, especially in the presence of enhanced de novo lipogenesis due to muscle insulin resistance.[89,90,104,105] The rising liver fat concentrations would cause steadily increasing hepatic insulin resistance with decrease of insulin's effectiveness in restraining liver glucose production. The resultant slight increase in fasting plasma glucose concentrations would induce compensatory increase in fasting plasma insulin concentrations. Insulin would further stimulate de novo lipogenesis, creating a cycle in the liver. As liver fat concentrations steadily increase, the rate of export of triglyceride to the rest of the body would increase. Once subcutaneous fat stores were replete, fat would be oversupplied to ectopic sites, including the pancreas. Given that human β cells avidly take up fatty acids[106] and that this inhibits glucose stimulated insulin secretion,[58,59,107] the hypothesis postulated a single process of interacting vicious cycles leading to both hepatic insulin resistance and β-cell dysfunction. Importantly, the hypothesis predicted that the type 2 diabetes state could return to normal if the initiating factor of excess liver fat was corrected. This correction would permit tracking of the changes in underlying pathological processes, which would be the same in reverse during onset of type 2 diabetes.

acids and that this occurs only in genetically susceptible β cells. The genetic nature of β-cell susceptibility to fat in humans is reflected by observed impairment of β-cell function after a 4-day lipid infusion only in those with a family history of type 2 diabetes[58,59] and in the atypical expression of the fatty acid transporter CD36 in those susceptible to type 2 diabetes.[95] This observation has recently been supported by fine mapping of loci related to type 2 diabetes.[54] Confusion about the role of increased fatty acid supply to pancreatic islets has arisen by focus upon plasma non-esterified fatty acids, which are increased only modestly in people at risk of type 2 diabetes.[96] The major route of delivery of fatty acids to all tissues is hydrolysis from plasma lipoprotein triglyceride in the capillary endothelium. Islet cells are known to take up fat avidly,[97] and it is known that intraislet fat closely reflects total pancreatic fat content in both humans and rodents.[98,99]

Unifying the pathophysiological observations

As muscle insulin resistance diverts meal-derived glucose to de novo lipogenesis, a major link exists with decreased β-cell function. De novo lipogenesis produces palmitic acid, the saturated fatty acid that is the most potent in decreasing β-cell function.[87,88]

Investigation into separate causes of the β-cell defect and insulin resistance has not explained how these factors could conspire to bring about type 2 diabetes. A seminal step forward was taken with the recognition of the extent to which removal of excess hepatic fat could decrease liver insulin resistance without change in muscle insulin resistance (figure 1).[89] Hepatic insulin resistance prevents full expression of insulin's action in restraining hepatic glucose output. Both hepatic insulin resistance and excess liver fat content are present before onset of type 2 diabetes[100,101] yet moderate weight loss was shown to bring about complete normalisation of both abnormalities with rapid normalisation of fasting plasma glucose.[89] These findings, along with other studies of liver fat and liver insulin resistance,[89,90,102,103] laid the basis for the twin cycle hypothesis of causes of type 2 diabetes (figure 2).[104]

Testing the twin cycle hypothesis

The hypothesis postulated that the underlying pathophysiological changes observed during a return to typical glucose metabolism would reflect in reverse order the causal processes that led to type 2 diabetes onset (figure 1). The counterpoint study was designed as a stringent but efficient means of achieving this state,[40] and the early results of testing the hypothesis have been reviewed.[17] Each step of the hypothesis was confirmed (figure 1). The high liver fat content typical of type 2 diabetes, hepatic insulin sensitivity, and fasting hepatic glucose output normalised. Hepatic export of triglyceride as VLDL normalised, intrapancreatic fat content decreased, and β-cell insulin secretion improved considerably, although not entirely back to rates seen in people without type 2 diabetes. A follow-up study established that when people with type 2 diabetes lost weight and returned to the non-diabetic state, these changes persisted after returning to isocaloric eating, although resolution of type 2 diabetes became less likely as duration of disease increased.[108] The study established, for the first time, that people with type 2 diabetes achieving adequate weight loss will normalise liver fat content and correct important abnormalities of lipid metabolism, but that not all individuals retain the ability to recover β-cell function.

Practical application of causal knowledge

Recognition of the importance of reaching remission to people with type 2 diabetes[109,110] led to the question of whether primary care nurses and dietitians provided with basic training in the dietary method could bring about lasting remission of type 2 diabetes. DiRECT, a 2-year randomised controlled trial designed to test this

question, reported significant weight loss of 10·6 kg at 1 year and 8·6 kg at 2 years, and remission rates of 46% at 1 year and 36% at 2 years.[56,111] Those who did not reach remission despite weight loss had a longer duration of type 2 diabetes even within the group of 0–6 years since diagnosis.[18] These findings are in accordance with observations after bariatric surgery.[112] The acceptability of the low-calorie liquid diet was again confirmed in this population-based study.[113]

DiRECT confirmed that weight loss decreased de novo lipogenesis to typical rates, as assessed by decreased plasma VLDL-1 triglyceride palmitate concentration and intrapancreatic fat content.[61] The total functional β-cell mass gradually returned over 12 months to rates similar to a matched non-diabetic control group and remained steady at 24 months (figure 1).[42] A small group (n=13) regained most of the weight lost and it was possible to observe the effect of this weight gain.[61] In those who gained weight and relapsed, plasma VLDL-1 triglyceride, total plasma triglyceride, and the palmitic acid content of VLDL-1 triglyceride all steadily increased during weight regain. This finding was associated with increase of pancreatic fat content to baseline concentrations and steady decline in first-phase insulin response causing return of the diabetic state.[61] Hence, the causative events leading to onset of type 2 diabetes were directly observed and found to be as hypothetically predicted. The change in hepatic lipid metabolism and indices of de novo lipogenesis caused by weight loss are the same whether brought about by dietary restriction alone or after bariatric surgery.[114,115]

The 5-year follow up results of DiRECT have been published.[116] Mean weight loss of 6·1 kg was maintained at 5 years with low-cost, routine health care provided by the National Health Service (NHS). 23% of those in remission at 2 years were in remission at 5 years and this group had been more successful in minimising weight regain, remaining an average of 8·9 kg below baseline weight. The previously noted improvement in wellbeing was maintained. Notably, those originally randomly assigned to the weight loss group had less than half of the serious adverse events compared with those randomly assigned to current best practice guidelines, despite weight regain in many. The DiRECT follow up was not long enough to show any effect on cardiovascular outcomes, but the 12-year follow up of Look AHEAD[117] showed approximate halving of both cardiovascular and chronic kidney disease onset even if remission had been transient.

Showing the simplicity of the pathological processes underlying type 2 diabetes and the feasibility of reversing these in routine clinical practice led to a pilot programme being launched by NHS England in 2020. The programme was designed to be provided by independent health coaches to avoid further burdening of the primary care sector. At 12 months, the low-calorie liquid diet with low-cost follow up achieved average weight loss of 9·4 kg by intention-to-treat in the first 1710 people.[118] A full, national type 2 diabetes remission programme for England was launched in 2023 in view of the likely individual and health economic benefits.[119] At present, the remission programme is restricted to people with BMI over 27 kg/m².

Twin cycle hypothesis and typical BMI

Currently, one in six people presenting with type 2 diabetes have a BMI below 27 kg/m² at diagnosis.[120] However, the epidemiological association between obesity, defined as BMI greater than 30 kg/m², and type 2 diabetes is now so strong that it is often assumed to be a cause and effect relationship.[121] In the 1970s, when the average weight of the UK population was considerably lower than at present, the Whitehall study[122] showed only a tenuous link between obesity and type 2 diabetes. Mean population BMI has since risen from 24 kg/m² to 28 kg/m².[11,123] Given that the relationship between BMI and type 2 diabetes is exponential,[124] a population increase in BMI is associated with a disproportionate increase in type 2 diabetes at higher BMI. The upward shift in population BMI distribution has led to the belief that obesity causes type 2 diabetes and that individuals with BMI in the lower range must have a non-fat associated cause for diabetes.

The UKPDS study[12] laid the basis for current understanding of type 2 diabetes, but the cohort studied reflected the background population. At the time of recruitment, the prevalence of obesity was 7%, with only 25% of the cohort having a BMI less than 30 kg/m² and 36% having a BMI of less than 25 kg/m².[10–12] These expressions of population association have no relevance for an individual; for example, women who increase their BMI from less than 22 kg/m² to 23–25 kg/m² have a four-fold increase in prevalence of type 2 diabetes compared with those who avoid weight gain.[124] Conversely, approximately 73% of individuals with BMI greater than 40 kg/m² do not have type 2 diabetes.[13]

The twin cycle hypothesis and subsequent studies on people with BMI greater than 27 kg/m² identified excess intraorgan fat as the driver of type 2 diabetes,[40,108] but also that the change in these underlying pathophysiological factors was the same across the wide BMI range studied. To explain these observations, the personal fat threshold hypothesis postulated that the maximum threshold at which the metabolically safe subcutaneous fat tissues could store triglyceride was a highly individual characteristic, and when surpassed ectopic fat would accumulate at all sites including the liver.[121] One known example of minimal capacity of subcutaneous fat storage is total lipodystrophy, which is accompanied by hepatic steatosis and high prevalence of type 2 diabetes.[125] In a rodent model of genetically determined total lipodystrophy, surgical implantation of fat pads from non-affected littermates allowed complete normalisation of the hepatic steatosis and glucose metabolism merely by increasing fat storage capacity.[126] The prediction that

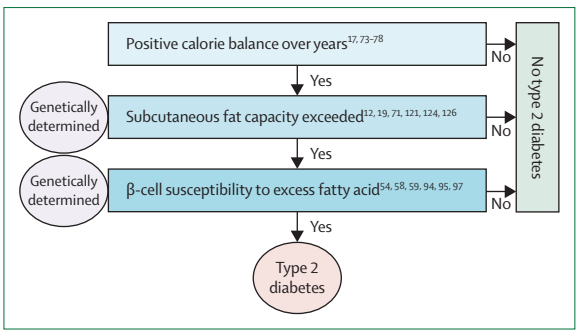

Figure 3: **Cause of type 2 diabetes**
People who take in more energy than they expend over many years could exceed their genetically determined capacity for safe subcutaneous storage. Only those who also have β cells susceptible to excess fatty acid delivery will develop type 2 diabetes. For susceptible individuals, the sole modifiable factor is energy balance.

subcutaneous fat capacity is genetically determined in humans was subsequently confirmed, with 53 genomic regions being associated.[71] Whether epigenetic modification is possible remains to be determined.

The hypothesis that the cause of type 2 diabetes did not differ in people who did not appear to have overweight was specifically tested in the ReTUNE study.[19] Because all previous studies had involved people with BMI greater than 27 kg/m², those with type 2 diabetes but with BMI from 21 kg/m² to 27 kg/m² were studied. The protocol involved successive 5% weight loss periods followed by 6 weeks of weight stability by stepwise weight loss to identify thresholds during weight stability.[19] The mean threshold to restore non-diabetic glucose control was reached at a weight loss of 6·5% with a wide individual range (5·5–10·2%). After the weight loss phase, an isocaloric diet of standard foodstuffs maintained the weight loss. In this group of people with lower range BMI but with type 2 diabetes, 70% achieved remission during the 12-month period of observation.[19, 127] Crucially, the pathophysiological mechanisms underlying this return to non-diabetic control were found to be identical to those in people with a higher BMI with type 2 diabetes. It was notable that liver fat content was three-fold greater in type 2 diabetes than in weight-matched controls across the combined BMI range of 21–45 kg/m², whereas in people with lower BMI the absolute concentration would have been classified as healthy by the conventional criteria for non-alcoholic liver disease. This upper boundary (<5·5%) was derived from a population with a mean BMI of 30 kg/m² and is inappropriate to apply in respect of classifying people of lower range BMI.[128] A recent study confirmed the 95% upper boundary for liver fat in this BMI range as just below 2%.[129]

Questions for future studies

The summary in figure 3 points very clearly to the crucial clinical question of how to minimise weight regain after successful weight loss. The 5-year follow up of DiRECT illustrates the problem of weight regain in the majority of participants, although that study was designed to be zero added cost for the NHS rather than to be as effective as possible. Increased support is required and apps to provide ongoing motivation and support might improve outcomes in a cost-effective manner. The potential role of new, powerful appetite suppressant drugs[130] in managing intermittent weight relapse must be explored. Taking in the additional consideration of prevention of diabetes and reversion from prediabetes,[45] wider investigation into how the energy intake of the whole population can be modified will be imperative.

The cellular mechanism whereby excess saturated fatty acids bring about loss of glucose dependent insulin release remains uncertain. Loss of specialised β-cell function by some process of dedifferentiation appears likely[131] but future studies are required to identify the exact mechanisms. Once glucose concentrations are raised, an additional metabolic stress upon the β cell is added. Although the rate of deterioration of glucose control in type 2 diabetes does not differ between well controlled or poorly controlled groups,[132] the interaction between excess glucose and fat supply to the β cell remains under-researched. In such studies it will be important to study separately β cells from humans or animals that are genetically susceptible to fat-induced dysfunction.[58,59,94]

Causes

Showing uniform cause of type 2 diabetes across the BMI range, as predicted by the twin cycle and personal fat threshold hypotheses, permits a summary of the development of type 2 diabetes. Individual susceptibility must be distinguished from cause. For any one person, genetic inheritance is fixed and the sole factor that determines the onset of type 2 diabetes is the accumulation of fat beyond an individual threshold in susceptible individuals (figure 3). The role of appetite in affecting food intake in any given environment must be acknowledged. Food intake varies between individuals, appears to be genetically controlled, and contributes to exceeding an individual's subcutaneous fat storage capacity.[71,133] It is likely that epigenetic modification, especially in utero or in early life, could affect expression of appetite.[134] As part of the environment, consumption of ultraprocessed foods leads to high energy intake.[135]

In contrast to the concept of heterogenous causes, the simplicity of fatty acid induced β-cell dysfunction is striking. The clearcut effects of saturated fatty acids upon β-cell function have been recognised for some time[63,88,136] and have been highlighted in recent reviews.[62,137] In vivo, weight loss induces a return to typical concentrations of plasma triglyceride and this is associated with a profound reduction in exposure of β cells to fatty acids coupled with recovery of function.[40,42,108] Related to this, a labile pool of intrapancreatic fat is decreased.[18,40,108] These

Search strategy and selection criteria

A systematic search in PubMed for English language articles published between Jan 1, 1960, and March 1, 2024 was carried out. Search terms included "type 2 diabetes," "aetiology", and "heterogeneity." Titles and abstracts were used to identify relevant studies. Studies were also sought within reference lists of eligible studies. I considered studies and trials that evaluated cause and remission of type 2 diabetes and explored relevant mechanisms.

pathophysiological studies provide a sound basis from which to understand the overwhelming evidence of overnutrition in causing type 2 diabetes.[73–78,124,138] Evidence for different causal subgroups of common type 2 diabetes is not strong. The concept inhibits research upon the clinically useful reversible factors that have been shown physiologically in humans.

Type 2 diabetes is a diagnosis of exclusion. The specific conditions of monogenic diabetes and slow onset type 1 diabetes currently account for a small proportion of those initially diagnosed as having type 2 diabetes in the populations who generally have overweight. These conditions could be expected to be more common in people who appear not to have overweight, and theReTUNE study of people specifically tested for monogenic diabetes and slow onset type 1 diabetes. Both monogenic diabetes and slow onset type 1 diabetes accounted for 8% of the initially recruited group.[19] Rarer conditions can present as hyperglycaemia including haemochromatosis, cystic fibrosis, and chronic pancreatitis but are usually diagnosed by other features.

Other distinct forms able to mimic type 2 diabetes might be discovered in future, but given the return to non-diabetic glucose control in approximately nine of ten people who reach 15 kg weight loss[61] and the behaviour of type 2 diabetes in whole populations,[74–77] it appears unlikely that new specific and yet unrecognised causes will account for more than a small percentage.

Conclusion

Identification of the role of excess fat inside liver and pancreas in the genesis of type 2 diabetes enables a simple statement: type 2 diabetes has a homogenous cause expressed in genetically heterogenous individuals.This statement is irrespective of BMI population standards and depends on exceeding a personal fat threshold. The heterogeneity in phenotypic characteristics and clinical course does not equate to heterogeneity in cause of the metabolic state. The predictions of the twin cycle hypothesis have repeatedly been confirmed. Weight loss of 10–15% by any means soon after onset of type 2 diabetes is highly likely to bring about remission of diabetes. This knowledge of the cause of type 2 diabetes is of immediate relevance to clinical management.

Contributors

I conceived the two hypotheses underlying the magnetic resonance-based research on causes of type 2 diabetes, evaluated published data, designed the low-calorie weight loss protocol, conducted studies, and authored the review. I reviewed and approved the final version.

Declaration of interests

I report grants from Diabetes UK, having received lecture fees and expenses from Eli Lilly and Abbott Laboratories outside the submitted work, and that I am an advisor to Fast800. I was a member of the Low Carbohydrate Working Group of the UK Government Scientific Advisory Committee on Nutrition and am a member of the advisory group for NHS England Type 2 Diabetes Path to Remission Programme, but all opinions expressed are personal and not representative of these bodies.

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References

1 Public Health England. 3·8 million people in England now have diabetes. 2023. https://www.gov.uk/government/news/38-million-people-in-england-now-have-diabetes (accessed June 29, 2024).
2 Ong KL, Stafford LK, Mclaughlin SA, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023; **402:** 203–34.
3 Schön M, Prystupa K, Mori T, et al. Analysis of type 2 diabetes heterogeneity with a tree-like representation: insights from the prospective German Diabetes Study and the LURIC cohort. *Lancet Diabetes Endocrinol* 2024; **12:** 119–31.
4 Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; **58:** 773–95.
5 Wesolowska-Andersen A, Brorsson CA, Bizzotto R, et al. Four groups of type 2 diabetes contribute to the etiological and clinical heterogeneity in newly diagnosed individuals: an IMI DIRECT study. *Cell Rep Med* 2022; **3:** 100477.
6 Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol* 1985; **248:** E286–91.
7 Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; **52:** 102–10.
8 Turner RC, Holman RR, Matthews D, Hockaday TD, Peto J. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 1979; **28:** 1086–96.
9 Vaag A, Lund SS. Non-obese patients with type 2 diabetes and prediabetic subjects: distinct phenotypes requiring special diabetes treatment and (or) prevention? *Appl Physiol Nutr Metab* 2007; **32:** 912–20.
10 Office for Health Improvements and Disparities. Obesity profile: short statistical commentary. 2023. https://www.gov.uk/government/statistics/obesity-profile-update-may-2023/obesity-profile-short-statistical-commentary-may-2023 (accessed Nov 12, 2023).
11 Rosenbaum S, Skinner RK, Knight IB, Garrow JS. A survey of heights and weights of adults in Great Britain, 1980. *Ann Hum Biol* 1985; **12:** 115–27.
12 UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 1991; **34:** 877–90.
13 Gregg EW, Cheng YJ, Narayan KM, Thompson TJ, Williamson DF. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004. *Prev Med* 2007; **45:** 348–52.
14 Hollenbeck CB, Chen Y-DI, Reaven GM. A comparison of the relative effects of obesity and non-insulin-dependent diabetes mellitus on in vivo insulin-stimulated glucose utilization. *Diabetes* 1984; **33:** 622–26.
15 Juhl CB, Bradley U, Holst JJ, Leslie RD, Yderstraede KB, Hunter S. Similar weight-adjusted insulin secretion and insulin sensitivity in short-duration late autoimmune diabetes of adulthood (LADA) and type 2 diabetes: action LADA 9 [corrected]. *Diabet Med* 2014; **31:** 941–45.

16 Reaven GM, Chen YD, Hollenbeck CB, Sheu WH, Ostrega D, Polonsky KS. Plasma insulin, C-peptide, and proinsulin concentrations in obese and nonobese individuals with varying degrees of glucose tolerance. *J Clin Endocrinol Metab* 1993; **76:** 44–48.

17 Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care* 2013; **36:** 1047–55.

18 Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab* 2018; **28:** 547–56

19 National Health Service. NHS Type 2 Diabetes Path to Remission Programme. 2024. https://www.england.nhs.uk/diabetes/treatment-care/diabetes-remission/ (accessed July 3, 2024).

20 Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2019; **16:** 35–56.

21 Gurung M, Li Z, You H, et al. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 2020; **51:** 102590.

22 He Y, Wu W, Zheng HM, et al. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nat Med* 2018; **24:** 1532–35.

23 Kootte RS, Vrieze A, Holleman F, et al. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes Obes Metab* 2012; **14:** 112–20.

24 Li HY, Zhou DD, Gan RY, et al. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients* 2021; **13:** 3211.

25 Zhou Z, Sun B, Yu D, Zhu C. Gut microbiota: an important player in type 2 diabetes mellitus. *Front Cell Infect Microbiol* 2022; **12:** 834485.

26 Guidone C, Manco M, Valera-Mora E, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* 2006; **55:** 2025–31.

27 Steven S, Hollingsworth KG, Small PK, et al. Calorie restriction and not glucagon-like peptide-1 explains the acute improvement in glucose control after gastric bypass in type 2 diabetes. *Diabet Med* 2016; **33:** 1723–31.

28 Yoshino M, Kayser BD, Yoshino J, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. *N Engl J Med* 2020; **383:** 721–32.

29 Shirakawa J, Fujii H, Ohnuma K, et al. Diet-induced adipose tissue inflammation and liver steatosis are prevented by DPP-4 inhibition in diabetic mice. *Diabetes* 2011; **60:** 1246–57.

30 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993; **259:** 87–91.

31 Nikolajczyk BS, Jagannathan-Bogdan M, Shin H, Gyurko R. State of the union between metabolism and the immune system in type 2 diabetes. *Genes Immun* 2011; **12:** 239–50.

32 Herder C, Brunner EJ, Rathmann W, et al. Elevated levels of the anti-inflammatory interleukin-1 receptor antagonist precede the onset of type 2 diabetes: the Whitehall II study. *Diabetes Care* 2009; **32:** 421–23.

33 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286:** 327–34.

34 Wright JJ, Eskaros A, Windon A, et al. Exocrine pancreas in type 1 and type 2 diabetes: different patterns of fibrosis, metaplasia, angiopathy, and adiposity. *Diabetes* 2023; published online Oct 26. https://doi.org/10.2337/db23-0009.

35 Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R. Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* 1996; **45:** 881–85.

36 Juge-Aubry CE, Somm E, Giusti V, et al. Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes* 2003; **52:** 1104–10.

37 Brismar K, Hilding A, Ansurudeen I, Flyvbjerg A, Frystyk J, Östenson CG. Adiponectin, IGFBP-1 and -2 are independent predictors in forecasting prediabetes and type 2 diabetes. *Front Endocrinol* 2023; **13:** 1092307.

38 Cooper GJS, Leighton B, Dimitriadis GD, et al. Amylin found in amyloid deposits in human type 2 diabetes mellitus may be a hormone that regulates glycogen metabolism in skeletal muscle. *Proc Natl Acad Sci USA* 1988; **85:** 7763–66.

39 Ueberberg S, Nauck MA, Uhl W, et al. Islet amyloid in patients with diabetes due to exocrine pancreatic disorders, type 2 diabetes, and nondiabetic patients. *J Clin Endocrinol Metab* 2020; **105:** 2595–605.

40 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54:** 2506–14.

41 Weir GC, Gaglia J, Bonner-Weir S. Inadequate β-cell mass is essential for the pathogenesis of type 2 diabetes. *Lancet Diabetes Endocrinol* 2020; **8:** 249–56.

42 Zhyzhneuskaya SV, Al-Mrabeh A, Peters C, et al. Time course of normalization of functional β-cell capacity in the diabetes remission clinical trial after weight loss in type 2 diabetes. *Diabetes Care* 2020; **43:** 813–20.

43 Cnop M, Hughes SJ, Igoillo-Esteve M, et al. The long lifespan and low turnover of human islet beta cells estimated by mathematical modelling of lipofuscin accumulation. *Diabetologia* 2010; **53:** 321–30.

44 Esser N, Utzschneider KM, Kahn SE. Early beta cell dysfunction vs insulin hypersecretion as the primary event in the pathogenesis of dysglycaemia. *Diabetologia* 2020; **63:** 2007–21.

45 Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. *Lancet* 2012; **379:** 2243–51.

46 He J, Watkins S, Kelley DE. Skeletal muscle lipid content and oxidative enzyme activity in relation to muscle fiber type in type 2 diabetes and obesity. *Diabetes* 2001; **50:** 817–23.

47 Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* 2002; **51:** 2944–50.

48 Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 2004; **350:** 664–71.

49 Szendroedi J, Schmid AI, Chmelik M, et al. Muscle mitochondrial ATP synthesis and glucose transport/phosphorylation in type 2 diabetes. *PLoS Med* 2007; **4:** e154.

50 Petersen KF, Dufour S, Savage DB, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc Natl Acad Sci USA* 2007; **104:** 12587–94.

51 Lim EL, Hollingsworth KG, Smith FE, Thelwall PE, Taylor R. Effects of raising muscle glycogen synthesis rate on skeletal muscle ATP turnover rate in type 2 diabetes. *Am J Physiol Endocrinol Metab* 2011; **301:** E1155–62.

52 Schrauwen-Hinderling VB, Kooi ME, Hesselink MK, et al. Impaired in vivo mitochondrial function but similar intramyocellular lipid content in patients with type 2 diabetes mellitus and BMI-matched control subjects. *Diabetologia* 2007; **50:** 113–20.

53 Batista TM, Haider N, Kahn CR. Defining the underlying defect in insulin action in type 2 diabetes. *Diabetologia* 2021; **64:** 994–1006.

54 Mahajan A, Wessel J, Willems SM, et al. Refining the accuracy of validated target identification through coding variant fine-mapping in type 2 diabetes. *Nat Genet* 2018; **50:** 559–71.

55 Udler MS, McCarthy MI, Florez JC, Mahajan A. Genetic risk scores for diabetes diagnosis and precision medicine. *Endocr Rev* 2019; **40:** 1500–20.

56 Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018; **391:** 541–51.

57 Roden M, Price TB, Perseghin G, et al. Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Invest* 1996; **97:** 2859–65.

58 Kashyap S, Belfort R, Gastaldelli A, et al. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. *Diabetes* 2003; **52:** 2461–74.

59 Storgaard H, Jensen CB, Vaag AA, Vølund A, Madsbad S. Insulin secretion after short- and long-term low-grade free fatty acid infusion in men with increased risk of developing type 2 diabetes. *Metabolism* 2003; **52:** 885–94.

60 Villasanta-Gonzalez A, Alcala-Diaz JF, Vals-Delgado C, et al. A plasma fatty acid profile associated to type 2 diabetes development: from the CORDIOPREV study. *Eur J Nutr* 2022; **61:** 843–57.

61 Al-Mrabeh A, Zhyzhneuskaya SV, Peters C, et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab* 2020; **31:** 233–49.

62 Lytrivi M, Castell AL, Poitout V, Cnop M. Recent insights into mechanisms of β-cell lipo- and glucolipotoxicity in type 2 diabetes. *J Mol Biol* 2020; **432:** 1514–34.

63 Cunha DA, Hekerman P, Ladrière L, et al. Initiation and execution of lipotoxic ER stress in pancreatic β-cells. *J Cell Sci* 2008; **121:** 2308–18.

64 Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabetes* 1988; **37:** 1020–24.

65 Borén J, Taskinen MR, Björnson E, Packard CJ. Metabolism of triglyceride-rich lipoproteins in health and dyslipidaemia. *Nat Rev Cardiol* 2022; **19:** 577–92.

66 Roma LP, Pascal SM, Duprez J, Jonas JC. Mitochondrial oxidative stress contributes differently to rat pancreatic islet cell apoptosis and insulin secretory defects after prolonged culture in a low non-stimulating glucose concentration. *Diabetologia* 2012; **55:** 2226–37.

67 Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; **6:** 361–69.

68 Zaharia OP, Strassburger K, Strom A, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019; **7:** 684–94.

69 Ostenson CG, Efendic S. Islet gene expression and function in type 2 diabetes; studies in the Goto-Kakizaki rat and humans. *Diabetes Obes Metab* 2007; **9** (suppl 2)**:** 180–86.

70 Suzuki K, Hatzikotoulas K, Southam L, et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature* 2024; **627:** 347–57.

71 Lotta LA, Gulati P, Day FR, et al. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. *Nat Genet* 2017; **49:** 17–26.

72 Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; **316:** 889–94.

73 Himsworth HP. Diet in the aetiology of human diabetes. *Proc R Soc Med* 1949; **42:** 323–26.

74 Franco M, Bilal U, Orduñez P, et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. *BMJ* 2013; **346:** f1515.

75 Joslin EP. The universality of diabetes: a survey of diabetes mortality in Arizona. *J Am Med Assoc* 1940; **115:** 2033–38.

76 Hrdlička A. Physiological and medical observations among the Indians of southwestern United States and north Mexico. *BAE* 1908; **34:** 1–460.

77 Knowler WC, Bennett PH, Hamman RF, Miller M. Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester, Minnesota. *Am J Epidemiol* 1978; **108:** 497–505.

78 Schulz LO, Bennett PH, Ravussin E, et al. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care* 2006; **29:** 1866–71.

79 Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 1990; **113:** 909–15.

80 Martin BC, Warram JH, Rosner B, Rich SS, Soeldner JS, Krolewski AS. Familial clustering of insulin sensitivity. *Diabetes* 1992; **41:** 850–54.

81 Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. *N Engl J Med* 1990; **322:** 223–28.

82 Taylor R, Price TB, Katz LD, Shulman RG, Shulman GI. Direct measurement of change in muscle glycogen concentration after a mixed meal in normal subjects. *Am J Physiol* 1993; **265:** e224–29.

83 Carey PE, Halliday J, Snaar JEM, Morris PG, Taylor R. Direct assessment of muscle glycogen storage after mixed meals in normal and type 2 diabetic subjects. *Am J Physiol Endocrinol Metab* 2003; **284:** e688–94.

84 Macauley M, Smith FE, Thelwall PE, Hollingsworth KG, Taylor R. Diurnal variation in skeletal muscle and liver glycogen in humans with normal health and Type 2 diabetes. *Clin Sci* 2015; **128:** 707–13.

85 Consoli A, Nurjahan N, Gerich JE, Mandarino LJ. Skeletal muscle is a major site of lactate uptake and release during hyperinsulinemia. *Metabolism* 1992; **41:** 176–79.

86 Smith GI, Shankaran M, Yoshino M, et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. *J Clin Invest* 2020; **130:** 1453–60.

87 Morgan NG, Dhayal S, Diakogiannaki E, Welters HJ. The cytoprotective actions of long-chain mono-unsaturated fatty acids in pancreatic beta-cells. *Biochem Soc Trans* 2008; **36:** 905–08.

88 Pinnick K, Neville M, Clark A, Fielding B. Reversibility of metabolic and morphological changes associated with chronic exposure of pancreatic islet beta-cells to fatty acids. *J Cell Biochem* 2010; **109:** 683–92.

89 Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54:** 603–08.

90 Ravikumar B, Gerrard J, Dalla Man C, et al. Pioglitazone decreases fasting and postprandial endogenous glucose production in proportion to decrease in hepatic triglyceride content. *Diabetes* 2008; **57:** 2288–95.

91 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999; **281:** 2005–12.

92 Rudenski AS, Hadden DR, Atkinson AB, et al. Natural history of pancreatic islet B-cell function in type 2 diabetes mellitus studied over six years by homeostasis model assessment. *Diabet Med* 1988; **5:** 36–41.

93 McGarry JD. What if Minkowski had been ageusic? An alternative angle on diabetes. *Science* 1992; **258:** 766–70.

94 Lee Y, Hirose H, Ohneda M, Johnson JH, McGarry JD, Unger RH. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci USA* 1994; **91:** 10878–82.

95 Nagao M, Esguerra JLS, Asai A, et al. Potential protection against type 2 diabetes in obesity through lower CD36 expression and improved exocytosis in β-cells. *Diabetes* 2020; **69:** 1193–205.

96 Rebelos E, Seghieri M, Natali A, et al. Influence of endogenous NEFA on beta cell function in humans. *Diabetologia* 2015; **58:** 2344–51.

97 Noushmehr H, D'Amico E, Farilla L, et al. Fatty acid translocase (FAT/CD36) is localized on insulin-containing granules in human pancreatic beta-cells and mediates fatty acid effects on insulin secretion. *Diabetes* 2005; **54:** 472–81.

98 Tremmel DM, Feeney AK, Mitchell SA, et al. Hypertension, but not body mass index, is predictive of increased pancreatic lipid content and islet dysfunction. *Am J Transplant* 2020; **20:** 1105–15.

99 Lee Y, Lingvay I, Szczepaniak LS, Ravazzola M, Orci L, Unger RH. Pancreatic steatosis: harbinger of type 2 diabetes in obese rodents. *Int J Obes* 2010; **34:** 396–400.

100 Sattar N, McConnachie A, Ford I, et al. Serial metabolic measurements and conversion to type 2 diabetes in the west of Scotland coronary prevention study: specific elevations in alanine aminotransferase and triglycerides suggest hepatic fat accumulation as a potential contributing factor. *Diabetes* 2007; **56:** 984–91.

101 Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; **30:** 2940–44.

102 Kotronen A, Seppälä-Lindroos A, Bergholm R, Yki-Järvinen H. Tissue specificity of insulin resistance in humans: fat in the liver rather than muscle is associated with features of the metabolic syndrome. *Diabetologia* 2008; **51:** 130–38.

103 Yki-Järvinen H. Fat in the liver and insulin resistance. *Ann Med* 2005; **37:** 347–56.

104 Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* 2008; **51:** 1781–89.

105 Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab* 2002; **87:** 3023–28.

106 Lalloyer F, Vandewalle B, Percevault F, et al. Peroxisome proliferator-activated receptor alpha improves pancreatic adaptation to insulin resistance in obese mice and reduces lipotoxicity in human islets. *Diabetes* 2006; **55:** 1605–13.

107 Boucher A, Lu D, Burgess SC, et al. Biochemical mechanism of lipid-induced impairment of glucose-stimulated insulin secretion and reversal with a malate analogue. *J Biol Chem* 2004; **279:** 27263–71.

108 Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care* 2016; **39:** 808–15.

109 Steven S, Lim EL, Taylor R. Population response to information on reversibility of type 2 diabetes. *Diabet Med* 2013; **30:** e135–38.

110 James Lind Aliance. Diabetes (type 2). 2024. https://www.jla.nihr.ac.uk/priority-setting-partnerships/diabetes-type-2/top-10-uncertainties.htm (accessed June 29, 2024).

111 Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019; **7:** 344–55.

112 Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014; **311:** 2297–304.

113 Rehackova L, Araujo-Soares V, Steven S, Adamson AJ, Taylor R, Sniehotta FF. Behaviour change during dietary type 2 diabetes remission: a longitudinal qualitative evaluation of an intervention using a very low energy diet. *Diabet Med* 2019; **37:** 953–62.

114 Hierons SJ, Abbas K, Sobczak AIS, et al. Changes in plasma free fatty acids in obese patients before and after bariatric surgery highlight alterations in lipid metabolism. *Sci Rep* 2022; **12:** 15337.

115 Pooler BD, Wiens CN, McMillan A, et al. Monitoring fatty liver disease with MRI following bariatric surgery: a prospective, dual-center study. *Radiology* 2019; **290:** 682–90.

116 Lean MEJ, Leslie WS, Barnes AC, et al. 5-year follow-up of the randomised Diabetes Remission Clinical Trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study. *Lancet Diabetes Endo* 2024; **12:** 233–46.

117 Gregg EW, Chen H, Bancks MP, et al. Impact of remission from type 2 diabetes on long-term health outcomes: findings from the Look AHEAD study. *Diabetologia* 2024; **67:** 459–69.

118 Valabhji J, Gorton Y, Barron , et al. Early findings from the NHS Type 2 Diabetes Path to Remission Programme. *Lancet Diabetes Endocrinol* (in press).

119 Xin Y, Davies A, Briggs A, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/Counterweight-Plus weight management programme. *Diabetologia* 2020; **63:** 2112–22.

120 Centers for Disease Control and Prevention. Prevalence of total, diagnosed, and undiagnosed diabetes among adults: United States, 2013–2016. 2018. https://www.cdc.gov/nchs/products/databriefs/db319.htm (accessed June 29, 2024)

121 Taylor R, Holman RR. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. *Clin Sci* 2015; **128:** 405–10.

122 Jarrett RJ, Keen H, Fuller JH, McCartney M. Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). *Diabetologia* 1979; **16:** 25–30.

123 National Health Service. Health Survey for England 2019: overweight and obesity in adults and children. 2019. https://files.digital.nhs.uk/9D/4195D5/HSE19-Overweight-obesity-rep.pdf (accessed June 22, 2022).

124 Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; **345:** 790–97.

125 Petersen KF, Oral EA, Dufour S, et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest* 2002; **109:** 1345–50.

126 Kim JK, Gavrilova O, Chen Y, Reitman ML, Shulman GI. Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. *J Biol Chem* 2000; **275:** 8456–60.

127 Riddle MC, Cefalu WT, Evans PH, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care* 2021; **44:** 2438–44.

128 Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005; **288:** E462–68.

129 Petersen KF, Dufour S, Li F, Rothman DL, Shulman GI. Ethnic and sex differences in hepatic lipid content and related cardiometabolic parameters in lean individuals. *JCI Insight* 2022; **7:** e157906.

130 Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021; **385:** 503–15.

131 Brereton MF, Iberl M, Shimomura K, et al. Reversible changes in pancreatic islet structure and function produced by elevated blood glucose. *Nat Commun* 2014; **5:** 4639–40.

132 Turner RC, Holman RR, Cull CA, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53.

133 Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42:** 937–48.

134 Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000; **49:** 2208–11.

135 Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metab* 2019; **30:** 226.

136 Diakogiannaki E, Dhayal S, Childs CE, Calder PC, Welters HJ, Morgan NG. Mechanisms involved in the cytotoxic and cytoprotective actions of saturated versus monounsaturated long-chain fatty acids in pancreatic beta-cells. *J Endocrinol* 2007; **194:** 283–91.

137 Martin S, Sorokin EP, Thomas EL, et al. Estimating the effect of liver and pancreas volume and fat content on risk of diabetes: a mendelian randomization study. *Diabetes Care* 2022; **45:** 460–68.

138 Taylor R, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol* 2019; **7:** 726–36.

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